Summary of Arguments:

Testerman et al. describe a system for treating obstructive sleep apnea that stimulates muscles associated with the upper air passageway to open the airway. As Examiner correctly states, Testerman et al do not disclose the stimulation of the diaphragm.

For the following reasons, Applicant submits that it would not be obvious to modify Testerman et al. to provide diaphragm stimulation instead of upper airway stimulation as suggested by the Examiner: 1) Christopherson et al do not teach that hypoglossal stimulation and diaphragm stimulation are substantially equivalent; 2) in literature referred to by Christopherson et al., research showed that diaphragm stimulation would worsen the upper airway obstructions that the upper airway stimulation of Testerman et al, was intended to relieve (thus teaching away from combining Testerman et al. with diaphragm stimulation); and 3) upper airway stimulation and diaphragm stimulation are not functionally equivalent. Accordingly it is submitted that, one of ordinary skill in the art at the time of the invention would not be motivated to substitute the upper airway stimulation of Testerman et al. with diaphragm stimulation.

Christopherson et al. Do Not Provide A Disclosure of Functional Equivalence of Upper Airway and Diaphragm Stimulation

Examiner relies on Christopherson et al. col. 6, lines 30-37 for the proposition that a modification of the upper airway stimulation in Testerman et al with diaphragm stimulation would be obvious because diaphragm stimulation and upper airway stimulation perform substantially the same function. However, in col. 6, lines 30-37, Christopherson et al., with specificity, only equate the function of hypoglossal nerve stimulation with stimulation of "other upper airway nerves or muscles". With respect to diaphragm stimulation, Christopherson et al only state that diaphragm stimulation may be used to treat sleep apnea or other respiratory disorders. Apparently, this statement referring to diaphragm stimulation merely reflects that which was known at the time of Christopherson et al, (and as noted by Christopherson et al. col. 1, lines 13-21) i.e., diaphragm stimulation had been proposed, e.g., for use in treating central sleep apnea. (But such diaphragm stimulation would cause or worsen airway obstruction.) (See e.g., p. 363, col.1 and p. 365, Figure 4 of the Glenn article that was referred to by Christopherson et al. col.1, lines 13-21).

Christopherson et al. are otherwise silent on the application or function of diaphragm stimulation. The examples set forth in Christopherson et al. appear only to illustrate the functional aspect of or applications for upper airway stimulation. Diaphragm stimulation is only vaguely and generally mentioned without description of a functional application (excepting as noted in the referenced Glenn article referred to in col. 1, lines 13-21.) Accordingly, it is submitted that Christopherson et al. can only be understood to reflect what one of ordinary skill in the art would understand at the time as the function of diaphragm stimulation in treating sleep apnea or other respiratory disorders.

It was understood in the art at the time of Christopherson et al. that diaphragm stimulation would exacerbate airway obstruction while upper airway stimulation was believed to relieve upper airway obstruction.

The purpose and function of the upper airway stimulation in Testerman et al was to open the upper airway or to relieve upper airway obstructions. As understood at the time of Christopherson et al., diaphragm stimulation would exacerbate upper airway obstruction. Thus, upper airway stimulation and diaphragm stimulation were not understood to perform substantially the same function. Christopherson et al. do not contradict this. Christopherson et al. disclose that there are two kinds of sleep apnea: obstructive and central. See col. 1, line 13 to col. 2, line 32. Different treatment methods for the different kinds of apneas were identified by references in these portions of the description. Specifically, obstructive sleep apnea was believed to be treatable with stimulation to the hypoglossal nerve which activates upper airway muscles. See col. 1, line 22 to col. 2, line 32. Central sleep apnea was believed to be treatable with diaphragm stimulation as set forth in the Glenn article referred to in col. 1, lines 13 to 21 (a copy of the Glenn article is enclosed for Examiner's convenience). According to the Glenn article, diaphragm stimulation, rather than opening the airway, caused or increased obstruction "almost invariably". (This is believed to be due to diaphragm contractions creating a negative intrapleural pressure that would further close the airway.) Thus, diaphragm stimulation was believed at the time of Christopherson et al. to have an opposite effect on airway obstructions than was intended by the upper airway stimulation disclosed in Testerman et al.

Accordingly, it is submitted that at the time of Christopherson et al. and as described in Christopherson et al. through the Glenn article, diaphragm stimulation and upper airway stimulation were understood to be functionally disparate. It is further submitted that Chrispherson, through incorporation of the Glenn article as an exemplary method of treatment, teaches away from substituting the upper airway stimulation of Testerman with diaphragm stimulation.

Upper Airway Stimulation and Diaphragm Stimulation are not Functionally Equivalent

Functionally, upper airway stimulation and diaphragm stimulation are not equivalent. The diaphragm, as it contracts, creates negative intrapleural pressure that creates volume change and breath. The upper airway muscles do not create breath or lung volume change. These differences in functionality would lead one of ordinary skill in the art to use stimulation of upper airway and diaphragm stimulation in different ways or for different applications.

Claim Rejections – 35 USC § 103 – Testerman et al. ,Christopherson et al. and Geddes

Claims 56 and 97 stand rejected under 35 U.S.C. 103(a) as being obvious over the modified Testerman et al. (US 5,522,862), as applied to claims 5-6, 53-55, 57-58, 71-74, 94-96 and 98-122 above, or, in the alternative, under 35 U.S.C. 103(a) as obvious over the modified Testerman.et al. in view of Geddes et al. (US 4,827,935).

For the reason set forth above, Applicants submit that one of ordinary skill in the art would not have combined Testerman et al. and Christopherson et al. to provide the "modified Testerman". Applicant's additionally submit that Testerman et al. and Geddes would not be properly combinable. Geddes discloses phrenic nerve activation which elicits diaphragm response. As noted above, one of ordinary skill in the art would not have modified Testerman et al. which teaches upper airway stimulation to treat obstructive sleep apnea with diaphragm activation/phrenic nerve stimulation.

Conclusion

Applicant accordingly submits that claims 5, 6, 53-58, 71-74, 94-140 are patentable over the prior art relied on by Examiner and thus are in condition for allowance. An early and favorable action on the merits is respectfully requested.

Respectfully Submitted,

Dated: 8/03/2006

Susan M. Schmitt (Reg. No. 34,427)

PETERS, VERNY, JONES, SCHMITT & ASTON, LLP
425 Sherman Avenue, Suite 230
Palo Alto, CA 94306
Telephone: (650) 324-1677
Facsimile: (650) 324-1678
Customer No.: 23308

Diaphragm Pacing: Present Status*

WILLIAM W. L. GLENN
From the Department of Surgery and the Clinical Research Unit, Yale University School of Medicine, New Haven, Connecticut, U.S.A.

Following the development of an implantable electrical cardiac pacemaker activated by a remote radiofrequency (RF) transmitter for patients with heart block,[1] the RF technique was adapted to the stimulation of other excitable tissues.[2] Stimulation of the phrenic nerve to pace the diaphragm was applied first to patients with acute ventilatory insufficiency in 1964 and then, in 1966, to a patient with chronic ventilatory insufficiency.[3] Since that time, a diaphragm pacemaker has been implanted for ventilatory support in about 180 patients. Observations concerning the indications for pacing, the technique of the operation, and the results in the 50 patients comprising the Yale series is the subject of this report.†

Clinical Application

Diaphragm pacing is indicated for patients with chronic ventilatory insufficiency in whom function of the phrenic nerves, lungs and diaphragm is proven adequate to sustain ventilation by electrical stimulation. This includes certain patients with paralysis of respiratory muscles (quadriplegia), with central alveolar hypoventilation (CAH) and chronic obstructive pulmonary disease (COPD). Pacing is not indicated in cases of ventilatory insufficiency resulting from respiratory paralysis due to lower motor neuron lesions involving the phrenic nerve, from muscular dystrophy affecting the diaphragm, or from extensive parenchymal lung disease. Pacing is also not indicated for patients with acute ventilatory insufficiency, such as that following acute poisoning, surgical operation, or other conditions giving rise to short-term hypoventilation; these cases are treated by conventional ventilatory support methods, i.e., endotracheal intubation and positive pressure respiration.

Preoperative Screening Tests (Table I)

Proof of viability of the phrenic nerve is prerequisite to implantation of a neural electrode. There have been a number of patients with compression of the spinal cord without complete interruption of neural connection to higher centers who showed some voluntary motion of the diaphragm by fluoroscopy. In such cases, to determine that other viable phrenic neurons exist, the nerve in the neck is electrically stimulated percutaneously.[4] An electrode probe (usually available from the physiotherapist as part of the neural stimulation equipment), set to deliver 10 mA for 1 ms at a repetition rate of 1/sec, is directed behind the lateral border of the sternocleidomastoid muscle and moved up and down along the body of the anterior scalene muscle. The indifferent electrode, wet with saline, is placed behind the patient's neck. Location of the phrenic nerve is expedited by first identifying the brachial plexus lying lateral to the scalene muscle border; the phrenic nerve is found lying medial to the plexus. The response when most neurons are viable is a brisk contraction of the dia-

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†The major portion of this report was the subject of the Alton Ochsner Lecture for 1977 presented at Tulane University, New Orleans, LA.

Address for reprints: Dr. William W.L. Glenn, Department of Surgery, Yale University School of Medicine, 333 Cedar Street, New Haven, Connecticut 06510, U.S.A.

Table I.

Screening Tests for Candidates for Diaphragm Pacing

1. **Respiratory center function:**
   a) Ventilatory response to normocapnic hypoxia, hypercapnic hyperoxia and hypercapnic hypoxia
   b) Ventilatory response to p-100 airway occlusion test
   c) Arterial blood gas levels at rest and during sleep
   d) Urinary phosphoryl transferase enzyme levels (Leigh's disease)
2. **Lung function:**
   a) Routine pulmonary function tests
   b) Xenon^{133} perfusion and ventilation scans
   c) Maximum hyperventilation
   d) Flow-volume curve measurements
3. **Phrenic nerve and diaphragm function:**
   a) Voluntary movement of diaphragm observed at fluoroscopy
   b) Tests for nerve viability. Diaphragm response to:
      1) Percutaneous stimulation of phrenic nerves in the neck
      2) Transvenous stimulation of phrenic nerve in the thorax
      3) Direct stimulation of phrenic nerve at operation
   c) Phrenic nerve conduction study
4. **For presence of upper airway obstruction:**
   a) Upper airway resistance studies
   b) Monitored overnight sleep study to identify sleep apnea

phragm of at least several centimeters. A slight contraction of only a centimeter or less usually indicates viability of just a few neurons rather than failure of the probe to make good contact with the nerve. The absence of contraction when stimulating in the anatomical location of the nerve nearly always means non-viability of the nerve. If there is doubt that the probe locates the nerve, direct exploration is planned along with preparations to apply the nerve electrode should a viable nerve be found.

Phrenic nerve conduction time is also measured preoperatively. The normal conduction time from neck to diaphragm has been 7 to 10 ms. Prolongation beyond 12 ms may be an indication of serious local or systemic disease.[5,6]

In patients without total respiratory paralysis, hypoventilation is proven by the demonstration of chronic hypoxemia and carbon dioxide retention. Arterial blood gas determinations with the patient awake and resting quietly for one hour before withdrawal of the blood sample show a $PaCO_2$ of > 50 mm Hg and a PaO_2 of < 75 mm Hg; these values are more abnormal during sleep.

An overnight sleep study is routinely carried out to document the presence of hypoventilation through the monitoring of arterial blood gases, and to detect the presence of sleep apnea of central origin or due to upper airway obstruction (UAO).[7]

Diaphragm motion is measured under the fluoroscope. In the supine position and with maximum voluntary effort exerted, the normal diaphragm should descend on inspiration 5 to 10 cm from functional residual capacity.

Pulmonary function is evaluated in nonparalyzed patients. Evidence of mild to moderate impairment due to restrictive or obstructive lung disease is common in patients with longstanding CAH. Where obstructive lung disease is the predominant cause of hypoventilation, the decision to pace the diaphragm is based on several factors: (1) rapid and progressive deterioration of ventilation as evidenced by an increasing number of episodes of respiratory failure requiring hospital admission for treatment; (2) intolerance to the administration of low-flow oxygen at times of ventilatory decompensation; (3) the presence of a domed diaphragm that descends at least 4 cm on maximum voluntary effort from functional residual capacity; and (4) improvement in arterial blood gas levels during voluntary hyperventilation.[8]

The Diaphragm Pacemaker

Briefly, the diaphragm pacemaker consists of four parts: a radiofrequency transmitter, an external coil or antenna, a radiofrequency receiver, and one or two phrenic nerve electrodes. The programmed RF pulses are transmitted via the antenna through the intact skin to the subcutaneously placed RF receiver where they are converted to electrical pulses and delivered via wire electrodes to the phrenic nerve. The electronic apparatus has been described in detail elsewhere.[9,10]*

*Avery Laboratories, Farmingdale, N.Y. 11735

Technique of Implantation of the Electrode-Receiver Assembly

In the 50 patients in our series (with the exception of two small children in whom it was implanted in the thorax), the phrenic nerve electrode was implanted in the neck. Local anesthesia was used in all but children and uncooperative adults. A tracheostomy, if well healed, was no contraindication to operations on the phrenic nerve, though special care was taken to isolate the tracheostomy site during the procedure.

Where bilateral pacing was required the two pacemakers were implanted at two separate operations 10 to 14 days apart.

Implantation of Phrenic Nerve Electrode (Cuff Electrode): A 4-inch transverse incision was made one inch above and parallel to the clavicle. This will be referred to as the upper incision. The sternoclavicular muscle, split longitudinally when of large size, was retracted medially to expose the internal jugular vein. The scalene fat pad adjacent to the vein was retracted laterally to expose the anterior scalene muscle. To locate the phrenic nerve, a bipolar nerve finder set at four to six volts was used to identify the nerve before it actually was visualized. The nerve was exposed where it crossed from the lateral to the medial side of the anterior scalene muscle. The scalene fascia over the nerve was carefully preserved. At the site selected for placement of the neural cuff (usually about the middle of the scalene muscle), parallel incisions were made 6 to 7 mm long through the scalene fascia, 2 to 3 mm on each side of the nerve. Care was taken to preserve the perineural blood supply. An over-and-over stitch of 4-0 Prolene®* was taken in the scalene fascia and muscle about 1 cm lateral to the nerve, opposite the parallel incisions in the fascia. This stitch was used to fix the heel of the electrode cuff in place. At this time in some cases, a similar stitch was taken 1 cm medial to the nerve and opposite the incision in the scalene fascia to fix the lip of the electrode. (However, frequently we prefer placing the stitches to fix the fascia and scalene muscle to the lip and heel of the cuff after the electrode is inserted behind the nerve.) A right-angled clamp was gently inserted through the incisions in the fascia behind the nerve to create a tunnel for the unipolar electrode with nerve cuff. A monofilament suture was attached to the silastic lip of the cuff and the other end threaded through the tunnel on the right-angled clamp, from the lateral to the medial side of the nerve where it was picked up with forceps and gently pulled to guide the cuff through the tunnel. Great care was taken to avoid undue manipulation of the nerve. When the cuff was properly placed the phrenic nerve lay freely in it on top of the platinum electrode. The Prolene® sutures placed to secure the cuff were tied to the cuff to hold it firmly in position (Fig. 1).

The technique to apply a bipolar nerve cuff electrode was somewhat different and was described elsewhere.[19,21]

Implantation of Radio Receiver: When the electrode cuff was securely affixed behind the nerve, a pocket for the receiver was formed as follows. A second transverse incision, referred to as the *lower* incision, was made 3 to 4 inches long at the costal margin in the mid or anterior axillary line. The pocket thus formed was developed cephalad about 4 inches deep and made wide enough to accept both receiver and indifferent plate electrodes. A third transverse incision, referred to as the *middle* incision, was made one to two inches long at the level of the fourth rib in the midclavicular line. This provided access to the silastic-covered wires from the cuff electrode above and the receiver below. The indifferent electrode, with its plate facing the undersurface of the skin, was implanted, via the *lower* incision, within the subcutaneous pocket and then attached to the anode electrode of the receiver *(marked with a red thread)*. The connection was secured with a monofilament plastic thread. The cathode electrode of the receiver and the electrode wires from the nerve cuff were then brought towards each other within subcutaneous tunnels. Subcutaneous passage of the cathode

*Prolene®, Ethicon Co., Somerville, N.J.

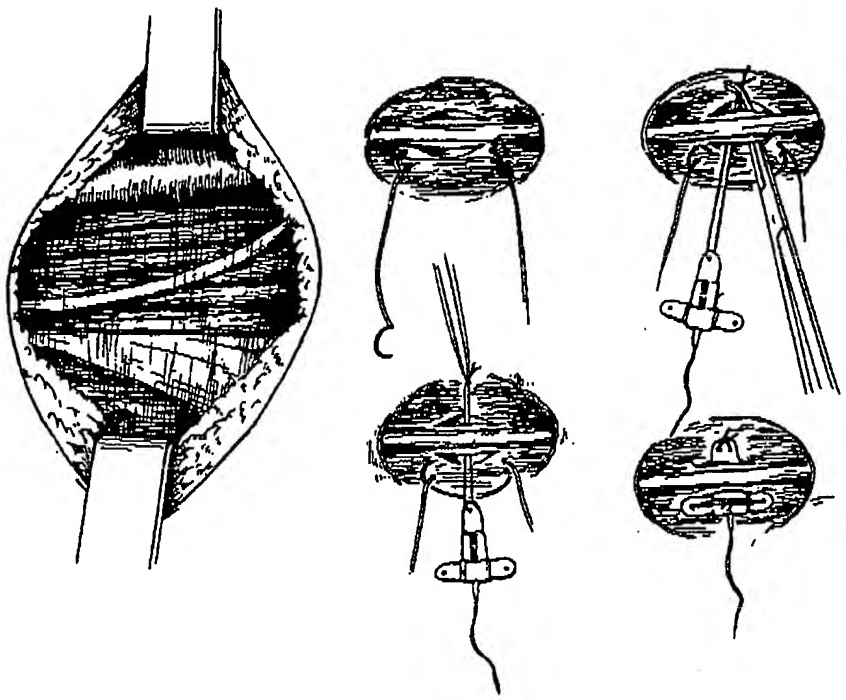

Figure 1. *Technique of applying unipolar electrode for diaphragm pacing to phrenic nerve in the neck.*

electrode of the receiver was facilitated by first pulling a plastic chest tube (#28F) subcutaneously from the *lower* incision then out of the *middle* incision. The terminal of the cathode electrode was inserted into the end of the tube for a short distance where it was held by a suture passed through the wall of the tube. When the tube was withdrawn through the *middle* incision, the electrode wire (except for its terminal segment) remained within the tunnel. The terminal tip of the electrode wire became accessible externally for connection to the terminal tip of the nerve cuff electrode which was passed, subcutaneously as above, from the upper to the *middle* incision. As the receiver electrode (cathode) was pulled through the subcutaneous tunnel (from the *lower* incision to the *middle* incision), the receiver, *with its copper coil directed towards the undersurface of the skin,* was advanced into the subcutaneous pocket to lie next to the indifferent plate electrode.

When bilateral stimulation was required the two receivers were implanted on opposite sides of the chest 15 cm apart. Attention was now turned to the connecting tips from the nerve cuff and the receiver lying outside the *middle* incision. The two electrode tips were connected and the connection was secured with a monofilament plastic ligature. This electrode junction and any excess of insulated wire were implanted in a Teflon®† (0.5 mil thick) bag in a subcutaneous pocket at about the level of the nipple for easy accessibility in the event of replacement of the receiver.[12] The integrity of the system was checked prior to closure of the wounds by diaphragm pacing using a sterile antenna placed on the skin over the receiver. Nerve-electrode contact was assured by flooding the neck wound with saline. All incisions were closed and dead space completely obliterated with multiple, interrupted sutures of plain catgut; care was taken not to incorporate the electrode wires in the sutures. The integrity of the system was checked once more by diaphragm pacing before the patient was allowed to leave the operating room.

Pacing Schedule

To provide time for the subsidence of postoperative edema, a regular schedule for stimulation of the nerve was not begun for at least ten days after implantation of the unit. Where two stimulators were required and were implanted separately about two weeks apart, pacing of each side was scheduled accordingly. At the start of pacing the patient was fluoroscoped and a base-line measurement made of diaphragm excursions and of that current which would initiate contraction of a hemidiaphragm (threshold) and that which would produce maximal contraction.

Ten to 14 days postoperatively and after a short (one to three hour) trial of pacing while awake, patients with central alveolar hypoventilation (CAH) without diaphragm paralysis were started on nightly pacing of 8-10 hours.

Quadriplegics, on the other hand, since their diaphragms in most cases were weakened from prolonged inactivity and required conditioning, had to be paced according to a schedule of gradually lengthening periods of stimulation. After the initial recovery period, pacing was done for five minutes every hour. Each side was paced individually. Tidal volumes were measured at the start and finish of each period of pacing. A respirometer allowing breath-by-breath measurement of tidal volume was indispensible during the conditioning period.* When the tidal volume at the end of the period was 75% or more of that at the beginning, the length of pacing could be increased. Usually we increased it by two minutes per hour per day until the diaphragm was being paced 30 minutes of each hour. The period of pacing on each side could then be lengthened through increments of five minutes per hour daily. Each period of pacing was followed by a similarly long rest period during which positive pressure ventilation was resumed. The early phase of diaphragm conditioning was done only during the waking hours, the respirator being used during sleeping. When a one-hour long period of pacing maintained an adequate minute volume, the pacing period was increased by 15-minute increments daily until a six-hour period was reached. At this point it was usually possible to increase pacing up to 12 hours on each side over the next week or two. When this amount of pacing maintained satisfactory minute volumes and normal arterial blood gases, the patient could be taken off the mechanical respirator completely. Such weaning usually took three to four months. During this time the threshold of the nerve to stimulation usually rose so that it became necessary to augment the current. Adjustment of current to provide maximal diaphragm movement was made with the aid of the fluoroscope. Excessive current was guarded against as it would hasten fatigue or possibly damage the nerve permanently.

Posture had a marked influence on minute volumes during pacing. The largest volumes were obtained with the patient in the supine position, especially when the paced side was slightly elevated. Volumes invariably decreased upon sitting or standing. This could be partially prevented by application of an abdominal binder to elevate the diaphragm and/or by pacing both sides simultaneously. Such bilateral pacing could usually be tolerated six to eight hours a day.

Once the maximal stimulation time was ascertained, one of several schedules for maintaining it was adopted. For those patients able to tolerate it, pacing of each hemidiaphragm, alternately for a 12-hour period, was selected. Alternate stimulation for shorter periods was preferred by some patients. A few preferred alternating pacing with each breath, for at least part of each 24 hours.

Continuous pacing of one or both hemidiaphragms could not be done indefinitely because of fatigue.[13] When constant respiratory support was obviously required for maintenance of adequate ventilation, unilateral or bilateral pacing was done for up to 16 hours and a mechanical means of respiration used for the remainder of the 24-hour period.

In all quadriplegics the tracheostomy tube had to remain in place for positive pressure breathing until full-time pacing was established, at which time a tracheostomy button was

*The Bourns Ventilation Monitor, available from Bourns, Inc., Life Systems Division, Riverside, California 92503, measures air-flow electronically and is an ideal instrument for monitoring diaphragm pacing.

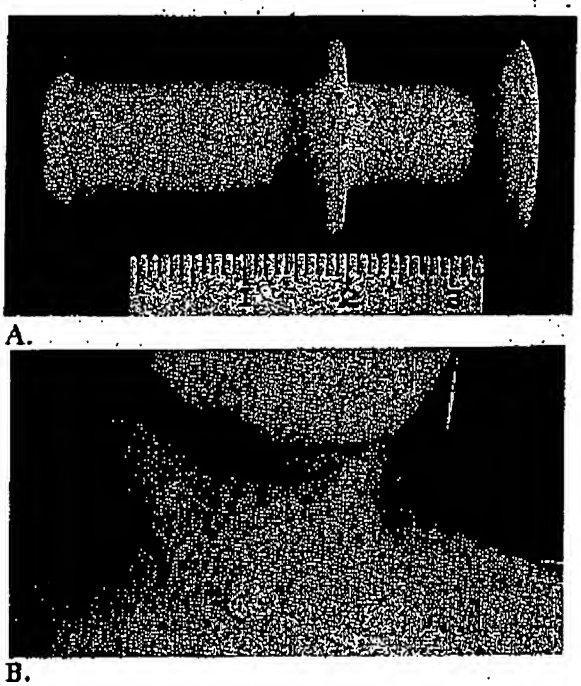

Figure 2. (A) *Plastic button to maintain patency of tracheostomy stoma. Obturator remains in place during waking hours but is removed during sleep to permit unobstructed breathing through stoma.* (B) *Patient with plastic button with obturator in place.*

substituted* (Fig. 2). Since these patients could not cough effectively, the tracheostomy stoma was kept patent for occasional suctioning and for reinstitution of positive pressure breathing in the event of pacemaker failure or inadequate ventilation, as was likely with severe bronchitis or pneumonia. In those patients with CAH complicated by UAO who required a tracheostomy, the tube also was replaced by a button when the tracheostomy wound had matured. The button obturator was removed during sleep to provide an unobstructed airway.

Pacing in small children presented special problems. Because of the wide swing of the mediastinum, very mobile in this age group, simultaneous bilateral pacing up to 16 hours daily was usually necessary. A tracheostomy has been required in all infants who are paced to provide an unobstructed airway.[14]

*Obtainable from the Quinton Instrument Co., Seattle, Washington. The diameter of the tracheal stoma and the distance from the skin to the trachea should be measured and the figures furnished the supplier.

Results

Central Alveolar Hypoventilation

Thirty-six of our 50 patients had CAH. The diagnosis was made on the basis of the following criteria: (1) clinical features of hypoventilation, which usually included cyanosis, polycythemia and cor pulmonale with right heart failure; (2) hypoxemia and hypercapnia, worsening during sleep; (3) hypoventilation during sleep, sometimes punctuated by periodic apnea; (4) near normal tests of ventilatory capacity; (5) diminished ventilatory response to induced hypoxemia and hypercapnia; and (6) either the absence of UAO during a sleep study or the persistence of hypoventilation following relief of the obstruction.[7,15]

Twelve of the 36 patients who had an organic lesion involving the respiratory center or cervical cord also had partial paralysis of the diaphragm or accessory muscles of respiration which contributed to hypoventilation. In one patient an organic lesion of the cervical cord (bilateral cervical cordotomy) without muscle paralysis was the cause for hypoventilation. In 17 patients hypoventilation secondary to an organic lesion involving the respiratory center, without muscle paralysis, was suspected or proved. In the remaining six patients no cause for CAH could be determined. Thirty-three patients underwent pacing of one hemidiaphragm for 8 to 12 hours during sleep. Three of the patients who were partially paralyzed required bilateral pacemakers for longer pacing since none had sufficient muscle strength for voluntary ventilation of more than a few hours. The age and sex of the patients and duration of pacing are listed in Tables II and III. The longest period of pacing for CAH to date is nine years; the patient, who had proven equinoencephalitis,[16] had a pacemaker applied to the left phrenic nerve in February 1969.

Pacing achieved long-term ventilatory support in all but one of the 36. Eleven patients died, nine from an underlying disease and two from pacemaker-related causes. The one patient unable to be supported died 6 months after

Table II.

Central Alveolar Hypoventilation with Paralysis of Respiratory Muscles: Patient Data

Etiology:	Cerebrovascular accident	5
	Medullary cyst or tumor	2
	Atlanto-occipital deformity	2
	Poliomyelitis	2
	Syringomyelia	1
	Bilateral cervical cordotomy	1*
Total cases:	13	
Age range:	17 to 71 years	
Sex distribution:	8 males; 5 females	
Duration of pacing:	Mean: 31 months	
	Range: 1 to 99 months	

*No respiratory muscle paralysis.

Table III.

Central Alveolar Hypoventilation without Paralysis of Respiratory Muscles: Patient Data

Etiology:	Encephalitis	7
	Unknown	6
	Trauma	4
	Leigh's disease	4
	Shock therapy	1
	Medullary cyst	1
Total cases:	23	
Age range:	2 to 67 years	
Sex distribution:	16 males; 7 females	
Duration of pacing:	Mean: 43 months	
	Range: < 1 to 106 months	

stimulation became ineffective following injury to the nerve by ethylene oxide used to sterilize the cuff electrode; in another, pacing failed to support ventilation following the administration of sedation for a minor operation.

Upper airway obstruction during sleep was detected in 18 of 24 patients with CAH who were specifically studied for this problem. Sixteen of the 18 suffered periodic episodes of UAO when not being paced; pacing invariably accentuated the obstruction (Fig. 3). In the other two who demonstrated prolonged episodes of central apnea when unpaced, pacing induced obstruction (Fig. 4).

A tracheostomy was recommended in 18 patients with obstruction and, in all but one, was accepted. Eleven of these had a follow-up overnight study. In eight, hypoventilation continued to be severe despite the tracheostomy while three showed only moderate hypoventilation during spontaneous respiration with the tracheostomy; pacing was continued to prevent the cumulative effects of persistent hypoventilation. Hypoventilation was relieved by pacing.

Quadriplegia

Paralysis of diaphragm and accessory muscles of respiration was the cause of hypoventilation in this group of 13 patients.

Ten patients had an injury to the cervical spinal cord while three had meningitis with possible herniation of the conus medullaris. Prior to being paced, all patients were supported on a mechanical ventilator for longer than a year, one patient for more than 11 years.

The age and sex of the patients and the duration of pacing are listed in Table IV. Ventilation was totally supported by diaphragm pacing in nine from this group. The longest period of such support was eight years, with each hemidiaphragm having been paced for 12 hours daily. Three of the nine required simultaneous bilateral pacing to achieve total support. However, it was necessary to take these patients off pacing from time to time because of diaphragm fatigue. Of the four patients who could be supported only part of the time by pacing, two were paced 16 to 18 hours daily; in the other two patients, pacing would not support ventilation for more than a few hours. Both of the latter patients had lesions involving the C_3, C_4 segments.

Three in this group died. One of those who could not be paced for more than a few hours died of respiratory complications while on a mechanical ventilator. A second patient with severe generalized spasms who had been paced bilaterally continuously for about six months died of brain damage resulting from an episode of circulatory arrest. A third patient whose respirations were totally supported by pacing for nearly two years, died from meningitis complicating a decubitus ulcer.

Chronic Obstructive Lung Disease (COPD)

We have applied diaphragm pacing to only

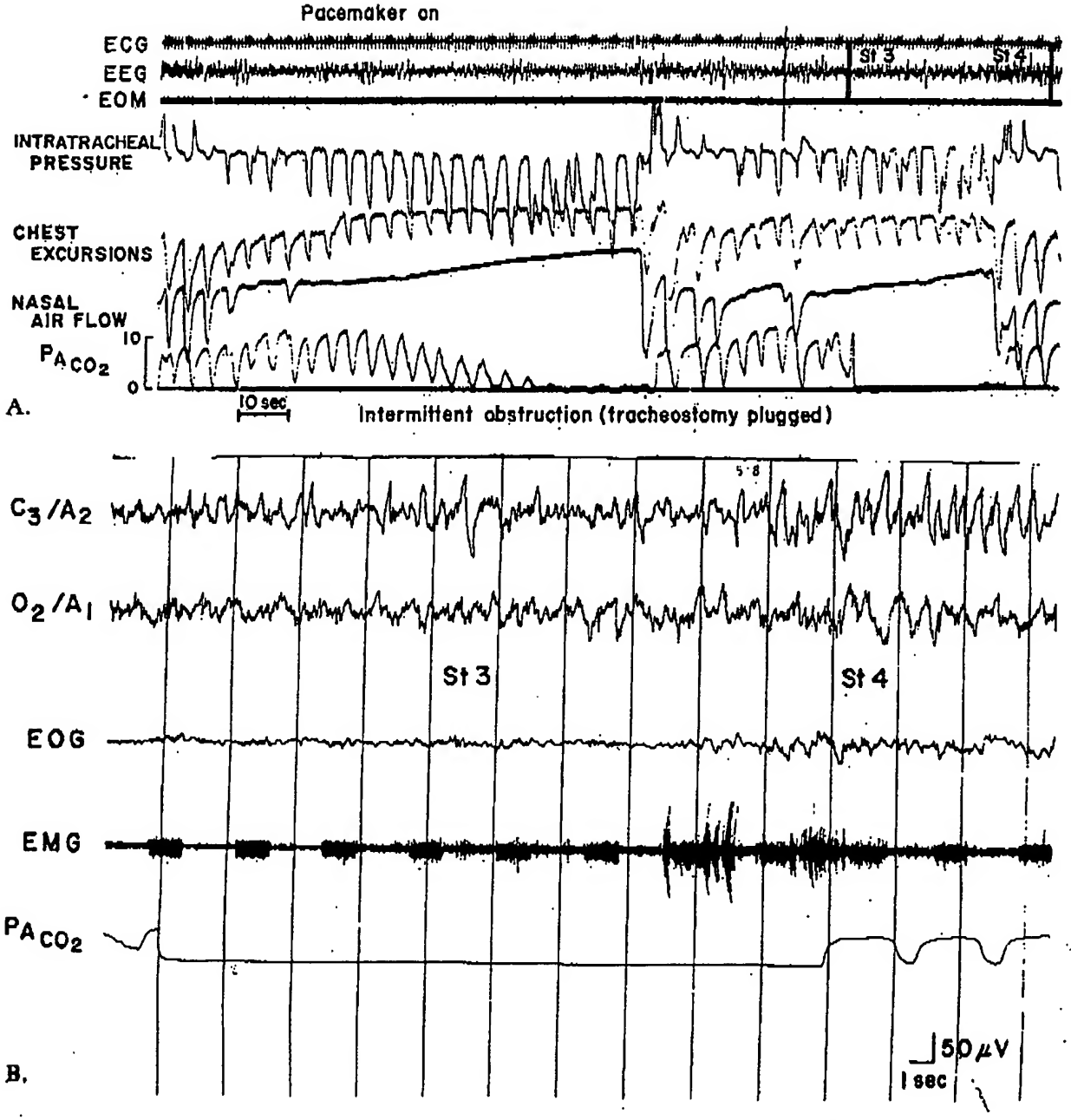

Figure 3. **(A)** *An increase in the duration and frequency of upper airway obstruction was demonstrated in patients who had evidence of obstruction before pacing was instituted. Note the prolonged period of obstruction (about 80 secs) during pacing. The intratracheal pressure becomes increasingly negative as the obstruction persists. The pacemaker artifact is superimposed on the ECG recording. Airway obstruction was completely relieved when the tracheostomy stoma was unobstructed.* **(B)** *This EEG recording represents the time between the two vertical lines in A. The patient was in sleep stages 3 and 4.*

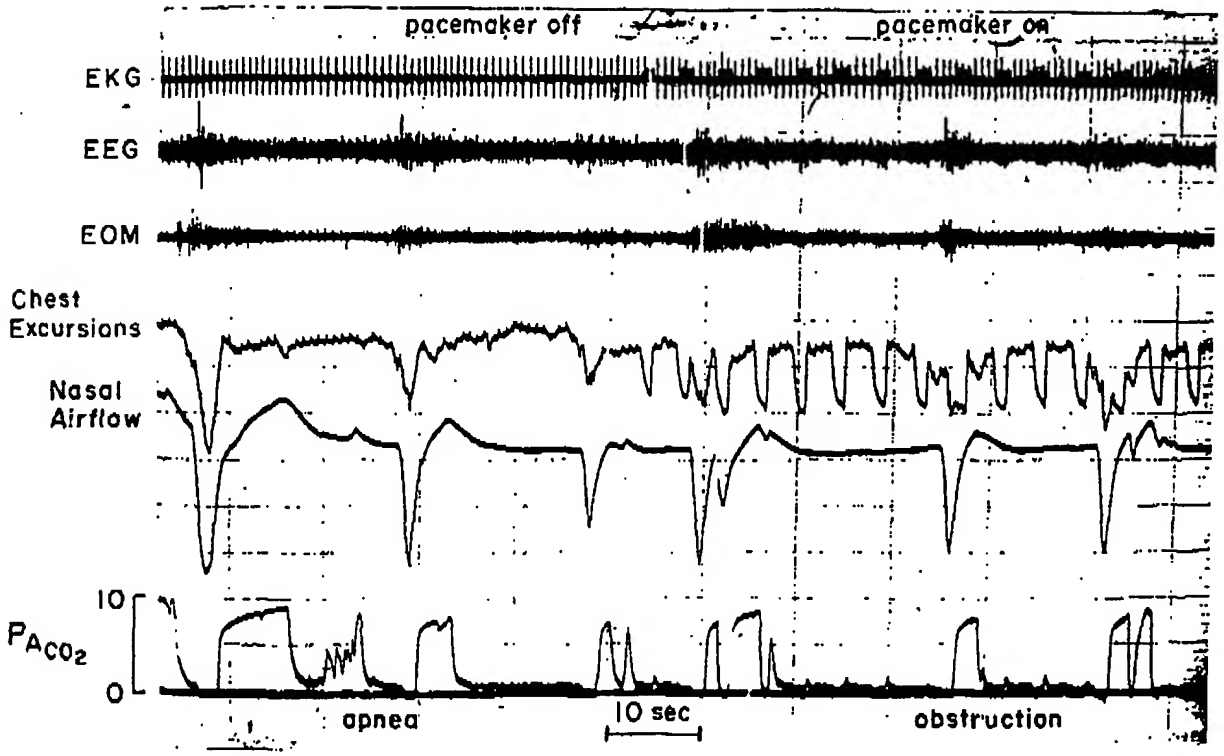

Figure 4. *Pacing-induced obstruction: Sleep study in a 53 year-old moderately obese male shows periodic central apnea during spontaneous respiration. This patient had no tracheostomy. On pacing of the diaphragm obstruction apnea replaced central apnea. A tracheostomy is required in such cases to realize the maximum benefit of pacing. Note the presence of chest excursions during periods of obstruction. Obesity may be contributng to obstruction during pacing. From Glenn, W.W.L., Gee, J.B.L., Cole, D.R., Farmer, W.C., Shaw, R.K., and Beckman, C.B.: Combined central alveolar hypoventilation and upper airway obstruction. Treatment by tracheostomy and diaphragm pacing. Am. J. Med., 64:50, 1978, with permission.*

Table IV.

Total Respiratory Paralysis (Quadriplegia): Patient Data

Etiology:	Trauma	10
	Meningitis	3
Total cases:	13	
Age range:	3 to 70 years	
Sex distribution:	9 males; 4 females	
Duration of pacing:	Mean: 33 months	
	Range: 2 to 86 months	

one COPD patient thus far—a 68 year-old male undergoing rapid deterioration secondary to repeated attacks of respiratory failure despite ideal medical treatment.[8] Hypoventilation in this patient was due not only to parenchymal lung disease but also to a diminution of the hypoxic drive by the administration of oxygen to combat hypoxia, and a diminished response to CO_2. A diminished respiratory response to life-threatening hypoxia indicated the need for diaphragm pacing to allow the safe administration of supplemental O_2 to avert this catastrophe (Table V).

Table V.

Chronic Obstructive Lung Disease: Patient Data

Etiology:	Chronic obstructive pulmonary disease 1
Total cases:	1
Age:	67 years
Sex:	1 male
Duration of pacing:	42 months

Discussion

There is both clinical and laboratory evidence that diaphragm pacing improves ventilation in patients with CAH. Clinically, there is increased alertness during the day, lessening of cyanosis, and disappearance of or diminution of right heart failure. The need for pacing was dramatically demonstrated in two patients with CAH, and in the patient with COPD, in whom the pacemaker receiver failed. None of these patients were immediately aware that pacing had stopped, but within a few days they became increasingly obtunded and finally comatose and required emergency cardio-pulmonary resuscitation. Following replacement of the faulty receiver and resumption of pacing, all three patients were again able to maintain adequate ventilation. When levels of hypercapnia and hypoxia comparable to those observed during sleep are produced in the awake patient, there is frequently no ventilatory response. Absence of such respiratory responses to life-threatening hypoxia is presumably the basis for the respiratory arrests during sleep in this group of patients, and indicates the need for diaphragm pacing to avert this catastrophe.[16]

Laboratory studies in patients with CAH support the clinical findings. Hypoxemia and hypercapnia are substantially lessened or eliminated by pacing.[9] Blood hematocrit levels are also reduced and pulmonary hypertension is relieved.[17]

Individuals who have hypoventilation on the basis of a space-occupying lesion of the brain stem can be expected to demonstrate evidence of other organ dysfunction as well. Muscle paralysis is common and in some cases contributes to hypoventilation. Particularly disabling is aspiration pneumonitis resulting from dysphagia secondary to hyperasthesia or anesthesia of the pharynx and paralysis of the pharyngeal muscles. Maximum rehabilitation will thus require, in addition to diaphragm pacing, a tracheostomy and gastrostomy and sometimes, if aspiration of saliva is a problem, surgical closure of the glottis.

The principle benefit of diaphragm pacing to the quadriplegic patient is release from dependence on a mechanical respirator. This usually means the ability to leave the hospital and to begin a meaningful rehabilitation program. The professional personnel caring for the patient throughout the operative and postoperative period are obligated to see to it that a rehabilitative program is promptly entered as soon as the expected maximum benefit from pacing is attained. It is not enough to free the patient from his tether to a mechanical respirator. We must see that he is placed in a rehabilitation program appropriate for his new mobile status.

As for the benefit expected from pacing the patient with COPD who meets the criteria referred to earlier in the section on screening, it should be stressed that the fundamental purpose of pacing is not amelioration of CO_2 retention nor augmentation of ventilation but prevention or reduction of the ventilatory depression during O_2 administration. Thus the proposed objective can be termed pacing-protected oxygenation.[7] This is particularly important during sleep. In patients with chronic bronchitis and emphysema, oxygenation improves cardiac and cerebral function and partially reduces pulmonary arterial hypertension. Additionally, as it did in our patient, oxygenation may prevent fatal apneic episodes when, later in the course of the disease, CO_2 retention and pulmonary function worsens.[7]

The evidence that pacing aided in the management of our patient with COPD is as follows. *First*, in the year prior to pacing, he was admitted to the hospital seven times for respiratory failure with CO_2 retention and profound hypoxemia. By contrast, after the institution of pacing there were four admissions for cardiorespiratory decompensation over 42 months. One of these admissions was precipi-

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tated by the patient's failure to take proper medications and another by failure of the receiver. *Second*, the patient received 42 months of approximately ten hours of both nightly O_2 (four l/min) and diaphragm pacing. This nocturnal oxygenation was accomplished without complications. *Third*, there was a consistent decline in hematocrit indicating adequate oxygenation. *Fourth*, the patient reported that pacing ameliorated his insomnia and daytime somnolence. *Fifth*, profound respiratory failure with coma occurred after a few days of no pacing.

Diaphragm pacing may not be successful for the following reasons:

First, poor selection of cases: Tantamount to successful ventilatory support is adequacy of function of the structures to be affected by electrical stimulation. Prior to implanting a diaphragm pacemaker, the functional status of the phrenic nerves, the lungs and the diaphragm must be ascertained. A list of the tests that should be routinely carried out are tabulated in Table I.

Second, injury to the phrenic nerve: Iatrogenic injury is the most common cause of damage to the nerve.[11] To minimize this most serious complication, the technique of operation detailed in this article should be carefully adhered to.

A unipolar electrode was employed initially for stimulation of the phrenic nerve but because local discomfort was reported during stimulation, it was abandoned in favor of a shielded bipolar model.[9] The bipolar electrode, with several minor modifications,[10] was applied to 51 phrenic nerves in our series. Histologic examination of seven cases, five from our own series, revealed varying degrees of pathologic change in most stimulated nerves.[11] Of signal importance, however, was the absence of nerve damage in two cases in which electrical stimulation had been applied for long periods, suggesting that changes seen in nerves in the other cases were the result of mechanical, not electrical factors. Using a stimulus of 5 mA (the usual stimulus is between 3 and 4 mA), and a pulse duration of 150 ms, the value of the charge (Q) to the phrenic nerve in our patients was 0.75 μC per impulse. Our electrode had a real area of 0.182 cm^2 and the charge density (QD) to the nerve was 4.1 μ C/real cm^2. This compares with a Q value of 0.5 μC and a QD value of 7.4 μ C/cm^2/phase which, when applied to the cerebellum, did not cause neural damage attributable to the electrical stimulation.[18]

In an attempt to lessen the chance of iatrogenic injury to the phrenic nerve, we reinvestigated the unipolar electrode. It was found in the experimental animal and in patients that careful shielding of the electrode placed behind the phrenic nerve made possible the application of current without causing symptoms indicative of spread of the current to adjacent tissues[20] (Fig. 1). Fifteen phrenic nerves in ten patients have now been stimulated with this electrode. The only difference noted between the stimulation parameters of the two types of electrodes was the slightly higher threshold to stimulation of the diaphragm obtained with the unipolar electrode. Histologic studies on nerves of animals stimulated with the unipolar electrode and of one patient who died after being paced continuously for about six months are in progress and will be reported separately.

Rarely, postoperative infection involves the phrenic nerve and requires removal of the cuff electrode. In the one patient we have seen with infection around the cuff, phrenic nerve conduction studies have shown prolongation of conduction time for many months after the nerve electrode was removed. The danger of infection is minimized by the use of meticulous aseptic technique at operation, restricting the operative procedure to one side at a time, delaying operation in the presence of fever or obvious sources of infection, and routinely administering prophylactic antibiotics.

Third, improper use of the pacemaker: This problem is frequently due to inadequate postoperative care and insufficient instructions to the patient. Unlike the electrical pacemaker for the heart, which after implantation can be expected to function in a predictable manner without further adjustment for at least several years, the diaphragm pacemaker will require a number of adjustments during the first year after implantation. A changing threshold to stimulation, usually a rise of 1 to 3 mA for the first few weeks after operation, requires repeated examination of the diaphragm under

fluoroscopy. At each of these examinations the knob pot setting for threshold to stimulation (the first visible contraction) and maximum contraction is determined and recorded. Stimulating current is regulated to not exceed that just required for maximum diaphragm contractions; injury to the nerve might otherwise occur.

After the first six months of stimulation, threshold and maximum levels usually remain about the same, rising or falling slightly for as long as they are monitored. In our series this has been, so far, up to eight years postoperatively.[11] A sudden or progressive rise to 7 mA or more in the threshold is cause for alarm. Phrenic nerve conduction times should be measured and if prolonged beyond 12 ms, nerve damage is likely. Pacing should be discontinued for a few days and the threshold and conduction time studies repeated. If still abnormal and if pacing is ineffective, removal of the cuff electrode will be necessary. At operation and prior to removal of the cuff, the viability of the nerve should be tested by direct stimulation of the nerve above and below the cuff.

Descent of the diaphragm is sometimes abrupt owing to failure of the electrical stimulus to activate the nerve at the beginning of the inspiratory cycle. With the aid of a transistor radio tuned to the frequency of the transmitter signal, the time of onset of diaphragm contraction in relation to the onset of the signal can be observed and, if there is a discrepancy, a slope adjustment can be made. An estimate of fatigue of the diaphragm can be made by measuring the latter's motion at the beginning and end of a pacing period. Another way of assessing fatigue, particularly in patients with a cuffed tracheostomy tube in place, is to measure minute volume at the beginning and end of a pacing period. Conditioning of the diaphragm in a patient with quadriplegia whose diaphragm has been paralyzed for months or years, although tedious and time consuming, cannot be rushed. Fatigue is inevitable if pacing is "forced." Tidal or minute volumes must be measured at the beginning and end of each pacing period, and the pacing period lengthened according to the diaphragm's ability to maintain 75% of the starting tidal or minute volume. Sometimes it is necessary to decrease the pacing period temporarily. Eventually a pacing schedule will be reached that will meet the requirements for attaining adequate ventilation over a certain period of time. Many combinations of pacing have been used to achieve this maximum without fatigue. In some patients pacing will provide adequate ventilation for only 12 to 16 hours daily. When total ventilatory support using each hemidiaphragm for alternate periods cannot be achieved without fatigue, it is tempting to pace both hemidiaphragms simultaneously and continuously. This is acceptable for a period of a few hours each day to allow sitting, but, on the basis of a large experience with animals and with three patients, the present state of the art dictates that simultaneous bilateral pacing, even when current delivered to the nerves is reduced, will eventually result in fatigue and inadequate ventilation. Radecki and Tomatis[21] report continuous bilateral pacing of an infant for 142 days, the patient dying of "bronchopneumonia." Liu et al[12] reviewed the phrenic nerve and diaphragm sections of this patient and concluded that signs of neurogenic atrophy of the diaphragm muscle were present. It is unknown if this atrophy was secondary to continuous pacing or to mechanical factors related to the nerve cuff.

Fourth, upper airway obstruction: Most of our patients with sleep apnea of central origin also demonstrated obstruction apnea[7] (Fig. 3). Unless the frequency of this association is appreciated and corrected by tracheostomy, the optimum benefits of diaphragm pacing will not be realized. Upper airway obstruction may also occur in patients with quadriplegia or with COPD.

Fifth, defective apparatus: The major problem with the present diaphragm pacemaker is in the design of the radio receiver. It is well known that epoxy will not protect electronic parts implanted in the body from fluid ingress. Failure of the receiver may be marked by abrupt cessation of pacing or by intermittent short periods of failure to pace. Occasionally failure is heralded by pain in the neck at the site of the nerve electrode or by a sudden fall in the threshold level. Unless patients are pacer dependent, as are quadriplegics, they may be unaware of cessation of pacing. It is important that all patients be told to watch for movement of the

abdomen when the pacer is turned on. It is not enough to detect the transmitter signal on the radio tuned to it, as the radio may pick up the signal without its being received by the receiver or phrenic nerve. As the respiratory centers are normally sensitive to hypercapnia and hypoxia in most quadriplegic patients, cessation of ventilation is appreciated promptly. An alarm system that can be activated by the quadriplegic patient must always be in readiness. Should pacemaker failure occur in a quadriplegic, pacing is immediately switched to the contralateral side and replacement made of the malfunctioning unit (usually the antenna or receiver) as soon as this is feasible. Unless the malfunctioning part can be replaced within 12 to 16 hours of beginning pacing on the contralateral side, positive pressure must be reinstituted. Prompt replacement of the receiver is indicated also in non-quadriplegic patients with CAH who may develop severe hypercapnia and hypoxia culminating in coma within 24 to 48 hours after pacing stops.

Breakage of the antenna or antenna connector to the transmitter occurs occasionally. An extra antenna should always be accessible for immediate replacement. Breakage of the nerve electrodes has been seen only once in our experience. Failure of electronic components of the transmitter has been uncommon. Failure of the transmitter is usually on the basis of premature exhaustion of the battery rather than malfunction of the electric components. The knob pot of the transmitter which is fragile and easily broken by manipulation, should be taped in position once the setting for pacing has been determined.

The normal rate of pacing in adults is 15 RPM with inspiration lasting about 1.3 sec or about one third of each respiratory cycle. An increase in the rate without adjustment of inspiration duration may increase the minute volume temporarily, but if continued for several hours it will cause fatigue of the diaphragm. In infants a faster rate is usually employed, up to 25 or 30 RPM, but the duration of inspiration is adjusted to occupy only one third of the respiratory cycle.

Sixth, in certain acute situations: Where pacing has been adequately supporting respiration, ventilatory failure may occur despite pacing due to further impairment of ventilatory function. Causes include (1) use of depressant drugs such as sedatives, tranquilizers, and pain relievers other than salicylates; (2) debilitating illness due to infection, tumors, and metabolic disorders, and following major operation; (3) acute pulmonary infection and pulmonary edema.

In the presence of the aforementioned acute causes of impairment of pulmonary function, one must not depend upon diaphragm pacing for ventilatory support. Pacing should be discontinued until the causes are removed. In the meantime, ventilatory support is provided by a mechanical ventilator.

Pacing will also fail in conditions marked by progressive disease or injury to the phrenic nerves, lungs and diaphragm.

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